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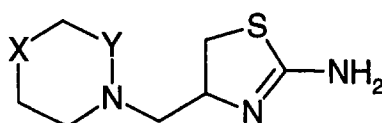
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USE OF 2-AMINO-THIAZOLINE DERIVATIVES AS INHIBITORS OF INDUCIBLE NO SYNTHASE

5 The present invention relates to the use of 2-amino-thiazoline derivatives of formula (I):



(I)

or their pharmaceutically acceptable salts as inhibitors of inducible NO synthase.

10 The invention provides for the use of 2-amino-thiazoline derivatives of formula (I) and their pharmaceutically acceptable salts for preparing pharmaceutical compositions intended for preventing and treating diseases involving abnormal production of nitrogen monoxide (NO) by induction of inducible NO synthase (NOS-2 or iNOS), the pharmaceutical compositions comprising the new 2-amino-thiazoline derivatives and their pharmaceutically acceptable salts and the new 2-amino-thiazoline derivatives and their pharmaceutically acceptable salts.

15 Nitrogen monoxide (NO) is a diffusible radical which is involved in numerous physiological and pathological processes. It is synthesized by oxidation of L-arginine, a reaction catalysed by a class of enzymes called nitrogen monoxide synthase or NO synthase (NOS), referenced in the international enzyme nomenclature system under the number E.C. 1.14.13.39.

20 Three isoforms of NOS, two of which are constitutive and one of which is inducible, are known:

- a neuronal NOS (NOS-1 or nNOS) was originally isolated and cloned from nerve tissue, where it is a constitutive enzyme. NOS-1 produces NO in response to various physiological stimuli, such as the activation of membrane receptors in accordance
25 with a mechanism dependent on calcium and on calmodulin.

- an inducible NOS (NOS-2 or iNOS) can be induced in response to immunological stimuli such as, for example, cytokines or bacterial antigens in various cells such as, for example, macrophages, endothelial cells, hepatocytes, glial cells, and a large number of other types of cells. The activity of this isoform is not regulated by calcium. Consequently, once induced, it produces large amounts of NO over prolonged periods.

- an endothelial NOS (NOS-3 or eNOS) is constitutive and calcium-calmodulin-dependent. It was originally identified in the cells of the vascular endothelium, where it generates NO in response to physiological stimuli such as the activation of membrane receptors.

The NO produced by the neuronal and endothelial constitutive isoforms (NOS-1 and NOS-3) is generally involved in intercellular signalling functions. For example, the endothelial cells which lie in the inner wall of blood vessels induce the relaxation of the underlying smooth muscle cells *via* the production of NO. It contributes in this way to the regulation of arterial pressure.

The NO produced in large amount by the inducible isoform, NOS-2, is involved *inter alia* in pathological phenomena associated with acute and chronic inflammatory processes in a wide variety of tissue and organs.

Excessive production of NO by induction of NOS-2 therefore plays a part in degenerative pathologies of the nervous system, such as, for example, multiple sclerosis, focal or global cerebral ischaemia, cerebral or spinal trauma, Parkinson's disease, Huntington's disease, Alzheimer's disease, amyotrophic lateral sclerosis, migraine, depression, schizophrenia, anxiety and epilepsy. Likewise, aside from the central nervous system, the induction of NOS-2 is involved in numerous pathologies with inflammatory components, such as, for example, diabetes, atherosclerosis, myocarditis, arthritis, arthrosis, asthma, irritable bowel syndrome, Crohn's disease, peritonitis, gastro-oesophageal reflux, uveitis, Guillain-Barré syndrome, glomerulonephritis, lupus erythematosus and psoriasis. NOS-2 has also been implicated in the growth of certain forms of tumours, such as, for example, epitheliomas,

adenocarcinomas or sarcomas, and in infections by gram-positive or gram-negative intracellular or extracellular bacteria.

In all situations where overproduction of NO is deleterious it therefore appears to be desirable to reduce the production of NO by administering substances capable of
 5 inhibiting NOS-2. However, given the important physiological parts played by the constitutive isoform NOS-3, in particular in regulating arterial pressure, it is paramount that the inhibition of the NOS-2 isoform should have the least possible effect on the NOS-3 isoform. This is because it is known that the administration of unselective inhibitors of the NOS isoforms results in vasoconstriction and in an
 10 increase in arterial pressure (Moncada, S., Palmer, R.M.J. and Higgs, E.A., Biosynthesis of nitric oxide from L-arginine: a pathway for the regulation of cell function and communication, *Biochem. Pharmacol.*, 1989, 38: 1709-1715). These effects on the cardiovascular system are detrimental in that they reduce the supply of nutrients to the tissues. Consequently, the present invention relates to compounds
 15 whose inhibitory activity on NOS-2 is significantly greater than its inhibitory activity on NOS-3.

Thiazoline-derived NOS inhibitors are described in particular in patent applications WO94/12165, WO95/11231 and WO96/14842.

The present invention relates to the use of 2-amino-thiazoline derivatives of formula
 20 (I) in which:

either Y is a methylene (CH₂) and X is selected from the following groups: O, NH, N-(C1-C4)alkyl, N-Bn, N-Ph, N-(2-Py), N-(3-Py), N-(4-Py), N-2-pyrimidyl, N-5-pyrimidyl, S, SO, SO₂, CH₂ or CHPh;

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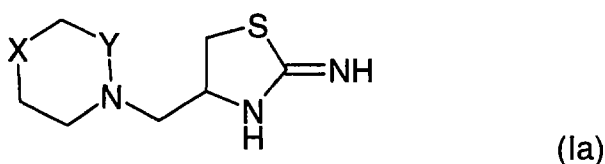
or Y is a carboxyl (C=O) and X is selected from the following groups: NH, N-Ph, N-(2-Py), N-(3-Py), N-(4-Py), N-2-pyrimidyl, N-5-pyrimidyl

for preparing medicaments useful for preventing or treating diseases involving abnormal production of nitrogen monoxide (NO) by induction of inducible NO synthase (NOS-2 or iNOS).

- 5 In the definitions above and below, the alkyl radicals contain 1 to 4 carbon atoms in a straight or branched chain. The abbreviations Bn, Py and Ph signify benzyl, pyridyl and phenyl, respectively.

- 10 The compounds of formula (I) have one or more asymmetric carbons and can therefore be present in racemic form or in the form of enantiomers and of diastereoisomers; these also form part of the invention, along with their mixtures.

Furthermore, the compounds of formula (I) may be present in the tautomeric form (Ia):



- 15 These tautomers also form part of the invention.

Among the compounds of formula (I) which are useful according to the invention, mention may be made of the following compounds:

4-morpholin-4-ylmethyl)-4,5-dihydro-1,3-thiazol-2-ylamine

4-(pyperazin-1-ylmethyl)-4,5-dihydro-1,3-thiazol-2-ylamine

- 20 4-(4-methyl-pyperazin-1-ylmethyl)-4,5-dihydro-1,3-thiazol-2-ylamine

their racemic mixtures, enantiomers, diastereoisomers and tautomers, and their pharmaceutically acceptable salts,

Among the compounds useful according to the invention and particularly preferred, mention may be made of the following compound:

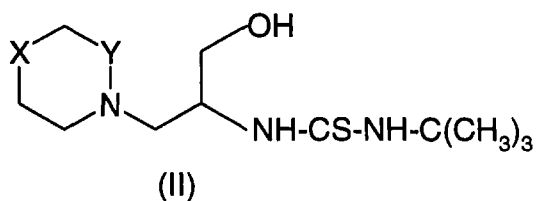
4-(4-methyl-piperazin-1-ylmethyl)-4,5-dihydro-1,3-thiazol-2-ylamine

its racemic mixture, its enantiomers and tautomers and their pharmaceutically acceptable salts.

The invention likewise relates to pharmaceutical compositions comprising as active principle a derivative of formula (I) for which either Y is a methylene (CH₂) and X is selected from the following groups: O, NH, N-(C1-C4)alkyl, N-Bn, N-Ph, N-(2-Py), N-(3-Py), N-(4-Py), N-2-pyrimidyl, N-5-pyrimidyl, S, SO, SO₂, CH₂ or CHPh; or Y is a carboxyl (C=O) and X is selected from the following groups: NH, N-Ph, N-(2-Py), N-(3-Py), N-(4-Py), N-2-pyrimidyl, N-5-pyrimidyl

and its racemic mixtures, enantiomers, diastereoisomers and mixtures thereof, its tautomer and its pharmaceutically acceptable salts.

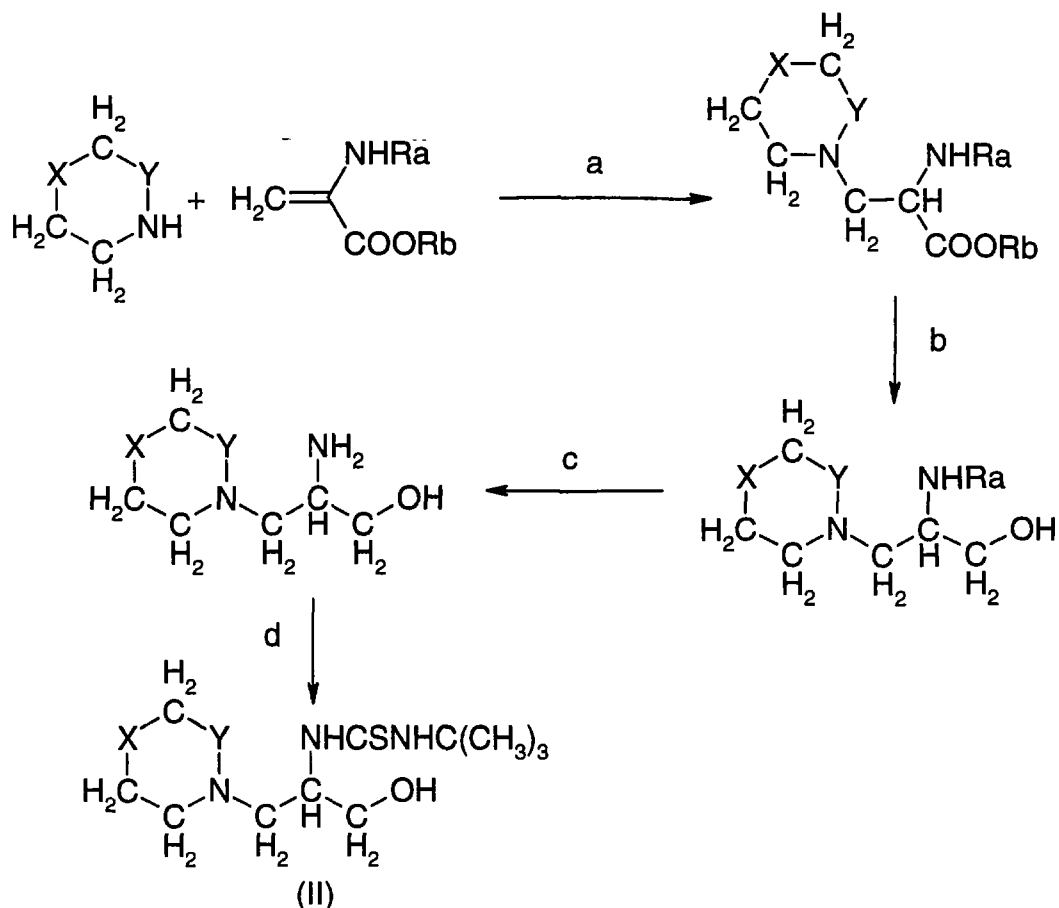
The compounds of formula (I) can be prepared by cyclizing a derivative of formula:



in which X and Y have the same meanings as in the formula (I).

This cyclization is generally effected by means of an acid such as hydrochloric acid in an aqueous medium at a temperature in the region of 100°C. Preference is given to using 6N hydrochloric acid.

The derivatives of formula (II) can be obtained in accordance with the following reaction scheme:



in these formulae, X and Y have the same meanings as in formula (I), Ra is a protective group for the amine function, such as those described by T.W. GREENE, Protective groups in Organic Synthesis, J. Wiley-Interscience Publication (1991), preferably an acetyl or *tert*-butoxycarbonyl radical, and Rb is a (1-4C)alkyl or alkoxycarbonyl radical, preferably methyl, ethyl or isobutyloxycarbonyl.

The reaction a is generally effected in the presence of a Lewis acid such as iron(III) trichloride in a solvent such as dichloromethane or acetonitrile at a temperature between 10°C and the boiling temperature of the reaction mixture. When X represents NH, X can be mono-protected beforehand by a protective group for the amine function, such as those described by T. W. GREENE, Protective groups in Organic Synthesis, J. Wiley-Interscience Publication (1991), preferably a *tert*-butoxycarbonyl radical.

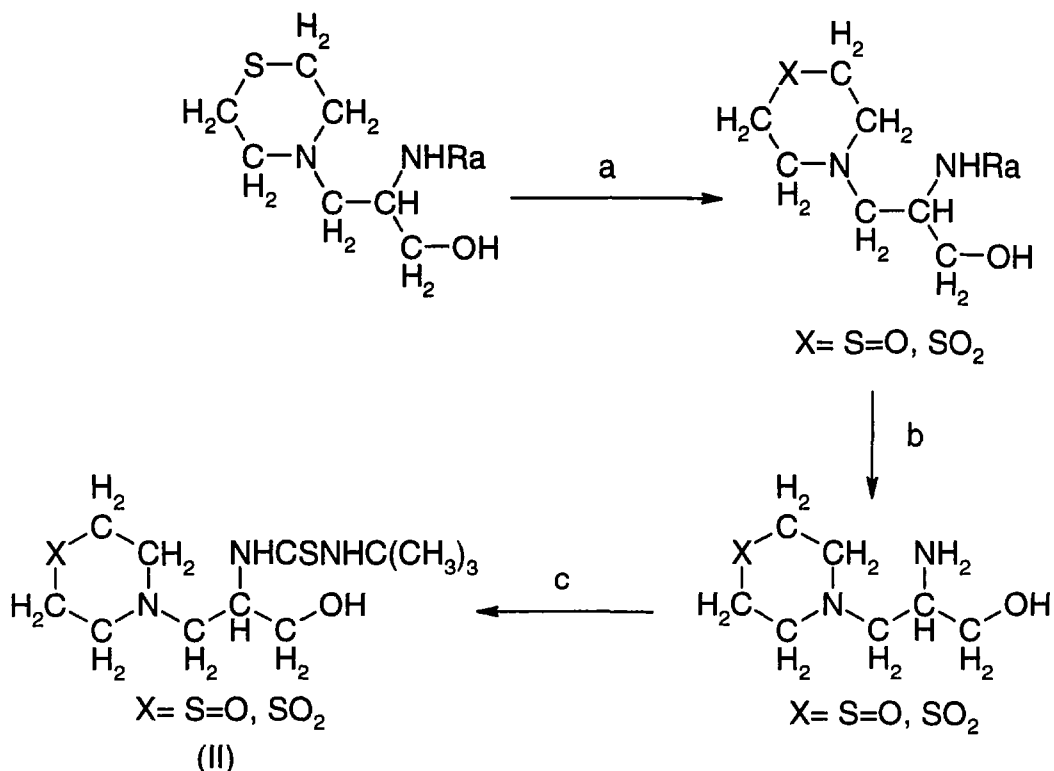
The reduction reaction b is effected preferably by means of a hydride such as sodium borohydride or lithium aluminium hydride in an aliphatic (1-4C) alcohol or terhydrofuran at a temperature between 0°C and 30°C.

5 The deprotection reaction c is effected with a deprotection agent of the compounds for which Ra is a protective group for the amine function, by any deprotection method known to a person skilled in the art, and in particular those described by T. W. GREENE, Protective groups in Organic Synthesis, J. Wiley-Interscience Publication (1991). Preferably, when the protective group is an acetyl radical, this reaction is effected by means of aqueous hydrochloric acid at a temperature in the
10 region of 100°C. When the protective group is *tert*-butoxycarbonyl radical this reaction is effected by means of hydrochloric acid in dioxane at a temperature in the region of 20°C.

The reaction d is effected by the action of *tert*-butyl isothiocyanate in an inert solvent such as an aliphatic (1-4C) alcohol (methanol or ethanol for preference) optionally in
15 the presence of a tertiary amine such as triethylamine at a temperature between 20°C and the boiling temperature of the reaction mixture.

The compounds of formula (I) for which X represents either SO or SO₂ can be obtained by direct oxidation of the compound of formula (I) for which X represents S. This oxidation is effected in accordance with known methods of oxidizing sulphur
20 compounds, such as those described by M. HUDLICKY, Oxidation in Organic Chemistry, ACS Monograph, 186, 252-263 (1990). For example, it is carried by the action of an organic peracid or a salt of an organic peracid (percarboxylic or persulphonic acid, especially perbenzoic acid, 3-chloroperbenzoic acid, 4-nitroperbenzoic acid, peracetic acid, pertrifluoroacetic acid, performic acid,
25 monoperphthalic acid) or a mineral peracid or a salt of a mineral peracid (for example, periodic acid or persulphuric acid) in an inert solvent such as a chlorinated solvent (chloroform or dichloromethane, for example) at a temperature of between 0 and 20°C. It is also possible to use hydrogen peroxide or a periodate (sodium periodate, for example) in an inert solvent such as a lower aliphatic alcohol, water or

a mixture of these solvents at a temperature between 0 and 20°C. These products can also be prepared from the corresponding compounds of formula (II), which are themselves obtained in accordance with the following reaction scheme:



- 5 The oxidation reaction a is effected in accordance with known methods of oxidizing sulphur derivatives, such as those described above.

- 10 The deprotection reaction b for the compounds for which Ra is a protective group for the amine function is effected by any method of deprotection known to the person skilled in the art, and especially those described by T.W. GREENE, Protective groups in Organic Synthesis, J. Wiley Interscience Publication (1991). Preferably, when the protective group is an acetyl radical, this reaction is effected by means of aqueous hydrochloric acid at a temperature in the region of 100°C. When the protective group is a *tert*-butoxycarbonyl radical this reaction is effected by means of hydrochloric acid in dioxane at a temperature in the region of 20°C.

The reaction c is effected by the action of tert-butyl isothiocyanate in an inert solvent such as an aliphatic (1-4C) alcohol (methanol or ethanol for preference) optionally in the presence of a tertiary amine such as triethylamine at a temperature between 20°C and the boiling temperature of the reaction mixture.

- 5 The compounds of formula (I) are isolated and can be purified by the usual known methods, for example by crystallization, chromatography or extraction.

The enantiomers of the compounds of formula (I) can be obtained by resolving the racemic mixtures, for example by chromatography on a chiral column in accordance with PIRCKLE W.H. et al., asymmetric synthesis, vol. 1, Academic Press (1983), or
10 by forming salts or by synthesis from chiral precursors. The diastereoisomers can be prepared according to the known conventional methods (crystallization, chromatography, or from chiral precursors)

The compounds of formula (I) can be optionally converted into addition salts with a mineral or organic acid by the action of such an acid in an organic solvent such as an
15 alcohol, a ketone, an ether or a chlorinated solvent. These salts also form part of the invention.

As examples of pharmaceutically acceptable salts mention may be made of the following salts: benzenesulphonate, hydrobromide, hydrochloride, citrate, ethanesulphonate, fumarate, gluconate, iodate, isethionate, maleate,
20 methanesulphonate, methylene-bis-b-oxynaphthoate, nitrate, oxalate, pamoate, phosphate, salicylate, succinate, sulphate, tartrate, theophyllineacetate and p-toluenesulphonate.

The compounds of formula (I) are inhibitors of inducible NO synthase or type-2 NO synthase (NOS-2) and thus are useful for preventing and treating disorders associated
25 with excessive NO production, such as multiple sclerosis, focal or global cerebral ischaemia, cerebral or spinal trauma, Parkinson's disease, Huntington's disease, Alzheimer's disease, amyotrophic lateral sclerosis, migraine, depression, schizophrenia, anxiety, epilepsy, diabetes, atherosclerosis, myocarditis, arthritis,

arthrosis, asthma, irritable bowel syndrome, Crohn's disease, peritonitis, gastro-oesophageal reflux, uveitis, Guillain-Barré syndrome, glomerulo-nephritis, lupus erythematosus, psoriasis, the growth of certain forms of tumours, such as, for example, epitheliomas, adenocarcinomas or sarcomas, and infections with gram-
5 positive or gram-negative intracellular or extracellular bacteria.

Their activities as NOS-2 and NOS-3 inhibitors were determined by measuring the conversion of [^3H]-L-arginine to [^3H]-L-citrulline with, respectively, an NOS-2 enzyme fraction extracted from lungs of rats or mice treated beforehand with lipopolysaccharides (10 mg/kg i.p. 6 hours before tissue harvesting) and with a
10 commercial preparation of bovine recombinant NOS-3. The compounds were incubated at 37°C for 20 to 30 minutes in the presence of 5 μM (for NOS-2 activity) or 10 μM (for NOS-3 activity) of [^3H]-L-arginine, 1 mM of NADPH, 15 μM of tetrahydropterin, 1 μM of FAD, 0.1 mM of DTT in a HEPES buffer (50 mM, pH 6.7) containing 10 $\mu\text{g/ml}$ of calmodulin and 1.25 mM of CaCl_2 when the NOS-3 activity
15 was measured. Incubation was stopped by adding cold HEPES buffer (100 mM, pH 5.5) containing 10 mM of EGTA and 500 mg of a cationic ion exchange resin (AG50W-X8, counterion: Na^+) to separate the [^3H]-L-arginine from the [^3H]-L-citrulline. After 5 minutes, during which the phases settled out, the residual radioactivity of the liquid phase was measured in a scintillation counter in the
20 presence of a suitable scintillation liquid. The yield of the recovery of the L-[^3H]-citrulline formed was able to be estimated using L-[^{14}C -ureido]-citrulline as external standard.

The NOS-2 or NOS-3 activity was expressed in picomole(s) of [^3H]-L-citrulline
25 formed per minute per milligram of protein present in the reaction mixture.

In this test on the NOS-2 enzyme, the IC_{50} of the compounds of formula (I) is less than or equal to 10 μM .

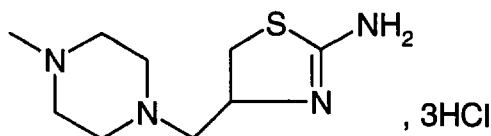
The selectivity is measured by the $\text{IC}_{50} \text{ NOS-3} / \text{IC}_{50} \text{ NOS-2}$ ratio. This selectivity is greater than 45.

The compounds of formula (I) are of low toxicity. Administered subcutaneously to mice, their LD₅₀ is greater than 40 mg/kg.

The examples below illustrate the invention.

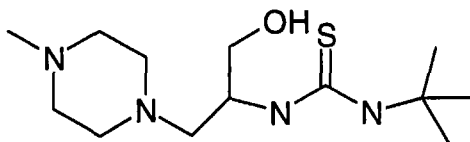
Example 1:

5 4-(4-Methylpiperazin-1-ylmethyl)-4,5-dihydro-thiazol-2-ylamine trihydrochloride



- 10 A suspension of 0.42 g de *N*-(*tert*-butyl)-*N'*-[2-hydroxy-1-(4-methylpiperazin-1-ylmethyl)ethyl]thiourea in 3.9 cm³ of 6N aqueous hydrochloric acid solution is heated at a temperature in the region of 100°C for 5 hours. After cooling, the reaction mixture is subsequently concentrated to dryness under reduced pressure (2 kPa) at a temperature in the region of 55°C. The meringue-like product obtained is dried in a
- 15 desiccator under vacuum (2 kPa) for 4 hours. This gives 0.47 g of 4-(4-methylpiperazin-1-ylmethyl)-4,5-dihydro-thiazol-2-ylamine trihydrochloride in the form of a highly hygroscopic meringue-like product off-white in colour. ¹H NMR spectrum (300 MHz, (CD₃)₂SO d₆ with addition of a few drops of CD₃COOD d₄, δ in ppm): from 2.55 to 2.90 (unresolved multiplet: 4H); 2.80 (s: 3H); from 2.95 to 3.30
- 20 (unresolved multiplet: 4H); from 3.30 to 3.60 (unresolved multiplet: 2H); 3.40 (dd, J = 11.5 and 5.5 Hz: 1H); 3.69 (dd, J = 11.5 and 7.5 Hz: 1H); 4.51 (mt: 1H).

N-(*tert*-Butyl)-*N'*-[2-hydroxy-1-(4-methylpiperazin-1-ylmethyl)ethyl]thiourea

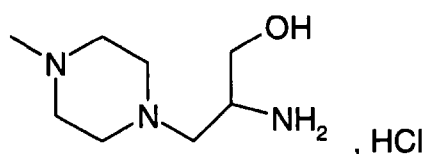


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A solution of 1 g of 2-amino-3-(4-methyl-piperazin-1-yl)-1-propanol hydrochloride in 20 cm³ of anhydrous ethanol and 1.43 cm³ of triethylamine is admixed with 0.78 cm³ of *tert*-butyl isothiocyanate. The reaction mixture is stirred under an inert atmosphere

at a temperature in the region of 20°C for 42 hours and then is heated at a temperature in the region of 50°C for 1 hour 30 minutes. After cooling to a temperature in the region of 20°C, the reaction mixture is evaporated under reduced pressure (2 kPa) at a temperature in the region of 30°C. The evaporation residue is taken up in 10 cm³ of water and 40 cm³ of dichloromethane. The aqueous phase is extracted with 2 times 30 cm³ of dichloromethane. The organic phases are combined, washed with 15 cm³ of water, dried over magnesium sulphate, filtered and then evaporated under reduced pressure (2 kPa) at a temperature in the region of 20°C. This gives 0.42 g of *N*-(*tert*-butyl)-*N'*-[2-hydroxy-1-(4-methylpiperazin-1-ylmethyl)ethyl]thiourea in the form of a white meringue-like product. Infrared spectrum between KBr plates 3279; 3075; 2939; 2806; 1533; 1459; 1359; 1295; 1204; 1010 and 821 cm⁻¹.

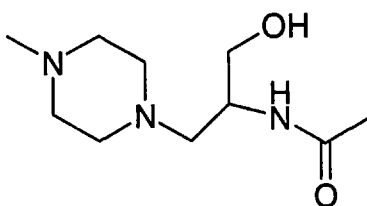
2-Amino-3-(4-methylpiperazin-1-yl)-1-propanol hydrochloride



A suspension of 0.89 g de *N*-[2-hydroxy-1-(4-methylpiperazin-1-ylmethyl)ethyl]-acetamide in 10.3 cm³ of 6N aqueous hydrochloric acid solution is heated at a temperature in the region of 100°C for 3 hours. After cooling to a temperature in the region of 60°C, the reaction mixture is filtered and the filtrate is evaporated under reduced pressure (2 kPa) at a temperature in the region of 60°C. This gives 1 g of 2-amino-3-(4-methylpiperazinyl)-1-propanol hydrochloride in the form of a sticky meringue-like product beige in colour.

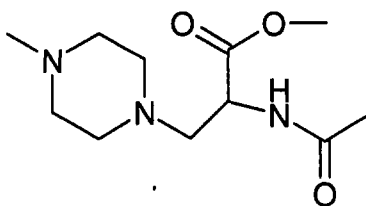
IR spectrum (KBr) 3337; 2955; 2637; 2522; 1617; 1457; 1062; 1009 and 962 cm⁻¹.

N-[2-Hydroxy-1-(4-methylpiperazin-1-ylmethyl)ethyl]acetamide



A solution under an inert atmosphere of 3.27 g of methyl 2-(acetylamino)-3-(4-methylpiperazin-1-yl)propanoate in 100 cm³ of anhydrous methanol is cooled to a temperature in the region of 10°C and then in spatula-tipfuls 0.76 g of sodium borohydride is added. The reaction mixture is stirred for 5 hours at a temperature in the region of 20°C and a further 0.26 g of sodium borohydride is added and stirring is continued for 38 hours. 5 cm³ of water are subsequently run into the reaction mass, which is subsequently concentrated under reduced pressure (2 kPa) at a temperature in the region of 30°C. The residual paste obtained is triturated with dichloromethane and the insoluble material is filtered off. The filtrate is concentrated under reduced pressure (2 kPa) at a temperature in the region of 20°C. The residue is purified by chromatography under argon pressure (60 kPa) on a column of silica gel (particle size 40-63 µm; diameter 5 cm; height 19 cm), eluting with successive dichloromethane-methanol-20% ammonia mixtures (98/2/0, 95/5/0.1, 90/10/0.2, 80/20/0.25, 50/50/0.25 by volume). The fractions containing the expected product are combined and concentrated under reduced pressure (2 kPa) at a temperature in the region of 40°C. This gives 0.92 g of *N*-[2-hydroxy-1-(4-methylpiperazin-1-yl)methyl]ethyl]acetamide in the form of a yellow liquid. IR spectrum CH₂Cl₂ 3621; 3429; 3352; 2944; 2803; 1657; 1513; 1460; 1284; 1050; 1011 and 816 cm⁻¹.

Methyl 2-(acetylamino)-3-(4-methylpiperazin-1-yl)propanoate



A solution of 8.57 g of methyl 2-acetamidoacrylate in 500 cm³ of dichloromethane, stirred under an inert atmosphere, is admixed with 6.65 cm³ of *N*-methylpiperazine and then with 0.97 g of iron trichloride and the mixture as a whole is stirred in the region of 20°C for 66 hours. Then 300 cm³ of an aqueous sodium sulphate solution are run into the reaction mixture, which is stirred vigorously and then filtered over Celite. After the phases have settled out and been separated, the organic phase is dried over sodium sulphate, filtered and then concentrated to dryness under reduced pressure (2 kPa) at a temperature in the region of 40°C to give an orange-coloured

liquid. The aqueous phase is extracted with 3 times 150 cm³ of dichloromethane and all the organic extracts are combined, dried over sodium sulphate and then concentrated under reduced pressure (2 kPa) at a temperature in the region of 20°C to give a yellow oil. The two intermediates obtained from the two organic phases are
5 combined and purified by chromatography under argon pressure (50 kPa) on a column of silica gel (particle size 40-63 µm; diameter 5 cm; height 25 cm), eluting with successive dichloromethane-methanol-20% ammonia mixtures (99/1/0, 97/3/0, 90/10/0.25, 80/20/0.25 by volume). The fractions containing the expected product are combined and concentrated under reduced pressure (2 kPa) at a temperature in the
10 region of 30°C. This gives 3.3 g of methyl 2-(acetylamino)-3-(4-methylpiperazinyl)propanoate in the form of a yellow liquid. IR spectrum CCl₄ 3437; 3318; 2941; 2798; 1749; 1685; 1499; 1458; 1374; 1286; 1204; 1168 and 1014 cm⁻¹.

The pharmaceutical compositions according to the invention are composed of a compound of formula (I) or an isomer or a tautomer or a salt of such a compound, in
15 the pure state or in the form of a composition in which it is combined with any other pharmaceutically compatible product, which may be inert or physiologically active. The medicaments according to the invention may be employed orally, parenterally, rectally or topically.

Solid compositions for oral administration which can be used include tablets, pills,
20 powders (gelatin capsules, cachets) or granules. In these compositions the active principal according to the invention is mixed with one or more inert diluents, such as starch, cellulose, sucrose, lactose or silica, under a stream of argon. These compositions may also comprise substances other than the diluents, for example one or more lubricants such as magnesium stearate or talc, a dye, a coating (coated
25 tablets) or a varnish.

Liquid compositions for oral administration which can be used include pharmaceutically acceptable solutions, suspensions, emulsions, syrups and elixirs containing inert diluents such as water, ethanol, glycerol, vegetable oils or liquid paraffin. These compositions may comprise substances other than the diluents, for
30 example wetting products, sweeteners, thickeners, flavourings or stabilizers.

The sterile compositions for parenteral administration may preferably be aqueous or non-aqueous solutions or suspensions or emulsions. As the solvent or vehicle it is possible to employ water, propylene glycol, a polyethylene glycol, vegetable oils, especially olive oil, injectable organic esters, for example ethyl oleate, or other
5 suitable organic solvents. These compositions may also contain adjuvants, especially wetting agents, isotonicity agents, emulsifiers, dispersants and stabilizers. Sterilization may be effected in a number of ways, for example by aseptic filtration, by incorporating sterilizing agents into the composition, by irradiation or by heating. They may also be prepared in the form of sterile solid compositions which can be
10 dissolved at the time of use in sterile water or any other injectable sterile medium.

The compositions for rectal administration are suppositories or rectal capsules which contain, in addition to the active product, excipients such as cocoa butter, semi-synthetic glycerides or polyethylene glycols.

The compositions for topical administration may be, for example, creams, lotions, eye
15 drops, mouth washes, nasal drops or aerosols.

In human therapy the compounds according to the invention are particularly useful for treating and/or preventing multiple sclerosis, focal or global cerebral ischaemia, cerebral or spinal trauma, Parkinson's disease, Huntington's disease, Alzheimer's disease, amyotrophic lateral sclerosis, migraine, depression, schizophrenia, anxiety
20 and epilepsy, diabetes, atherosclerosis, myocarditis, arthritis, arthrosis, asthma, irritable bowel syndrome, Crohn's disease, peritonitis, gastro-oesophageal reflux, uveitis, Guillain-Barré syndrome, glomerulo-nephritis, lupus erythematosus, psoriasis, the growth of certain forms of tumours, such as, for example, epitheliomas, adenocarcinomas or sarcomas, and infections by gram-positive or gram-negative
25 intracellular or extracellular bacteria.

The doses depend on the desired effect, on the duration of treatment and on the administration route used; they are generally between 1 mg and 100 mg per day via the oral route for an adult, with unit doses ranging from 0.5 mg to 50 mg of active substance.

Generally speaking, the doctor will determine the appropriate dosage as a function of the age, weight and all the other factors specific to the individual to be treated.

The examples below illustrate compositions according to the invention:

EXAMPLE A

- 5 In accordance with the usual technique, gel capsules containing a 50 mg dose of active product and having the following composition are prepared:

	- Compound of formula (I).....	50 mg
	- Cellulose	18 mg
	- Lactose	55 mg
10	- Colloidal silica	1 mg
	- Sodium carboxymethylstarch.....	10 mg
	- Talc	10 mg
	- Magnesium stearate	1 mg

EXAMPLE B

- 15 In accordance with the usual technique, tablets containing a 50 mg dose of active product and having the following composition are prepared:

	- Compound of formula (I).....	50 mg
	- Lactose	104 mg
	- Cellulose	40 mg
20	- Polyvidone	10 mg
	- Sodium carboxymethylstarch.....	22 mg
	- Talc	10 mg
	- Magnesium stearate	2 mg
	- Colloidal silica	2 mg
25	- Mixture of hydroxymethylcellulose, glycerine and titanium oxide (72-3.5-24.5) q.s. for 1 finished film-coated tablet weighing 245 mg	

EXAMPLE C

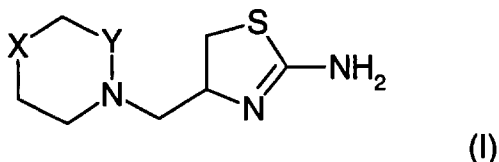
An injectable solution is prepared which contains 10 mg of active product and has the following composition:

	- Compound of formula (I).....	10 mg
	- Benzoic acid.....	80 mg
5	- Benzyl alcohol	0.06 ml
	- Sodium benzoate.....	80 mg
	- 95 % ethanol	0.4 ml
	- Sodium hydroxide.....	24 mg
	- Propylene glycol	1.6 ml
10	- Water..... q.s.	4 ml

The present invention also relates to the method of preventing and treating diseases involving abnormal production of nitrogen monoxide (NO) by induction of inducible NO synthase (NOS-2 or iNOS) by administering a compound of formula (I), its racemic mixtures, enantiomers, diastereoisomers and mixtures thereof, its tautomer
 15 and its pharmaceutically acceptable salts.

CLAIMS

1 Compounds of formula (I)



in which

5

either Y is a methylene (CH₂) and X is selected from the following groups: O, NH, N-(C1-C4)alkyl, N-Bn, N-Ph, N-(2-Py), N-(3-Py), N-(4-Py), N-2-pyrimidyl, N-5-pyrimidyl, S, SO, SO₂, CH₂ or CHPh;

10 or Y is a carboxyl (C=O) and X is selected from the following groups: NH, N-Ph, N-(2-Py), N-(3-Py), N-(4-Py), N-2-pyrimidyl or N-5-pyrimidyl

with the proviso that the (C1-C4)alkyl radicals contain 1 to 4 carbons in a straight or branched chain. The abbreviations Bn, Py and Ph signify benzyl, pyridyl and phenyl
15 respectively.

their racemic mixtures, enantiomers, diastereoisomers and mixtures thereof, their tautomers and their pharmaceutically acceptable salts.

2 Compound according to Claim 1, characterized in that it is selected from:

20 4-(morpholin-4-ylmethyl)-4,5-dihydro-1,3-thiazol-2-ylamine

4-(piperazin-1-ylmethyl)-4,5-dihydro-1,3-thiazol-2-ylamine

4-(4-methyl-piperazin-1-ylmethyl)-4,5-dihydro-1,3-thiazol-2-ylamine

their racemic mixtures, enantiomers, diastereoisomers and mixtures thereof, their tautomers and their pharmaceutically acceptable salts.

3 Compound according to any one of Claims 1 to 2 characterized in that it is selected from:

4-(4-methyl-piperazin-1-ylmethyl)-4,5-dihydro-1,3-thiazol-2-ylamine

5 its racemic mixtures, its enantiomers and tautomers and their pharmaceutically acceptable salts.

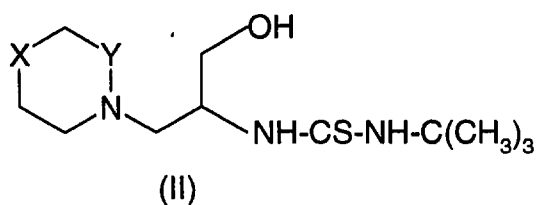
4 Compound according to any one of Claims 1 to 3 used to prepare a medicament.

5 Pharmaceutical composition characterized in that it comprises in a pharmaceutically acceptable medium a compound defined according to any one of Claims 1 to 3.

10 6 Medicament according to Claim 4 characterized in that it contains at least one compound defined according to any one of Claims 1 to 3 for its therapeutic application in the treatment of diseases involving abnormal production of nitrogen monoxide (NO) by induction of inducible NO synthase (NOS-2).

7 Medicament according to Claim 4 characterized in that it contains at least one
15 compound defined according to any one of Claims 1 to 3 for its therapeutic application in the treatment of Parkinson's disease.

8 Process for preparing compounds of formula (I) as defined in Claim 1 characterized in that a derivative of formula:

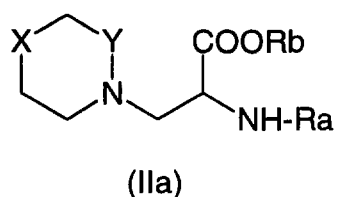


20 in which X and Y have the same meanings as in Claim 1 is cyclized.

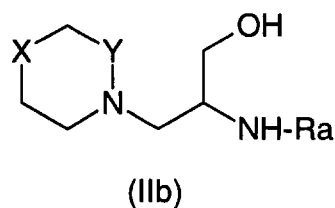
9 Preparation process according to Claim 8 characterized in that the cyclization takes place in an acidic medium at a temperature in the region of 100°C.

10 Preparation process according to Claim 9 characterized in that the acidic medium is preferably 6N hydrochloric acid

11 Process for preparing compounds of formula (II) as defined in Claim 8 and in which X and Y have the same meaning as in Claim 1 characterized in that a
5 compound of formula (IIa)

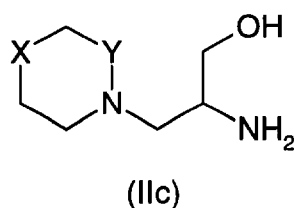


Ra being a protective group for the amine formation and Rb a (1-4C) alkyl radical or alkoxy carbonyl radical is subjected to the action of a reducing agent so as to give the compound of formula (IIb)

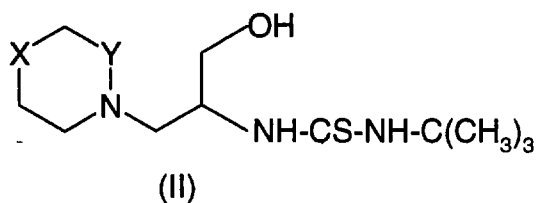


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which is subjected to the action of a deprotection agent so as to give a compound of formula (IIc)



15 which is subjected to the action of *tert*-butyl isothiocyanate so as to give a compound of formula (II)



12 As intermediates, the compounds of formulae II, IIa, IIb and IIc as defined in Claim 11 with the exception of the following products:

N-[2-hydroxy-1-(4-phenylpiperazin-1-ylmethyl)ethyl]thiobenzamide

5 methyl 2-(N-CBZ-amino)-3-morpholino-propionate

boc-DL-β-4-morpholiny)alanine methyl ester

methyl 2-acetamido-3-piperidinopropanoate

methyl 2-acetamido-3-morpholinopropanoate

ethyl 2-(N-benzyl-amino)-3-piperidinopropanoate

10 ethyl 2-(N-benzyl-amino)-3-morpholinopropanoate

13 As intermediates *N*-(*tert*-butyl)-*N'*-[2-hydroxy-1-(4-methylpiperazin-1-ylmethyl)ethyl]thiourea; *N*-[2-Hydroxy-1-(4-methylpiperazin-1-ylmethyl)ethyl]-acetamide; methyl 2-(acetyl-amino)-3-(4-methylpiperazin-1-yl)propanoate